



Mechanical ventilators and other medical devices for the Covid-19 crisis: initiatives, regulation and recommendations

Date: May 20th, 2020

Points of interest

- Requirements caused by COVID-19 could exceed the number of mechanical ventilators (or respirators) and other necessary devices available to treat affected patients. This has triggered interest in designing and manufacturing them (or components) through 3D printing technology or other processes.
- Safety of the medical devices/materials is one of the main aspects to consider. Therefore, the compliance with the essential requirements set by the current European Directive (Directive 93/42/CEE) concerning medical devices has to be guaranteed, which in a normal situation is credited with the compliance CE marking.
- According to this Directive:
 - Mechanical ventilators are medical devices class IIb.
 - T connectors (splitters) or similar devices used to multiply the capacity of the ventilators to 2-4 patients are not considered medical devices.
 - Masks and helmets with adaptors to use in CPAP are medical devices class II
 - Personalized products are considered to be medical devices, including those manufactured with 3D printing technology.
- All technologies or products considered medical devices with no CE marking should bear the exceptional use in the interest of health authorization of the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)¹ in order to be able to be used. They could also be used for clinical investigation. In both cases, a technical dossier should be available in order to list the technical specifications of the design, construction and control of the product and a risk assessment regarding the compliance of the product with the different essential requirements requested for its planned use and purpose. Furthermore, a follow-up of the clinical experience using the product and the surveillance of possible adverse incidents should take place.
 - Considering the situation with the Covid-19 pandemic, the AEMPS has drawn up a set of guidelines regarding **mechanical ventilators** on March 27th, 2020 for this **special approval procedure through a clinical investigation process**².
- **T connectors (splitters) or similar devices** can be used under certain clinical criteria and with previous validation of their functionality and approval from the hospital where they will be used. These products besides **multiplying the ventilation capacity** can be used to **manage the risk of any incident** that could occur by using the “innovative/low-cost” ventilators developed by the current crisis quickly connecting the patient to another respirator while the incidence with the first is solved.

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- **Masks and helmets with adaptors to use in CPAP** require the AEMPS' authorisation as compassionate use. The hospital that wants to use them has to request said authorisation.
- However, the CE marking is not requested for medical devices **manufactured “in house”** (that is, manufactured at the hospital to be exclusively used at that hospital) with 3D printing technology or any other technology³. In these cases, there is no commercial interest or other market options (due to the current extreme necessity situation) and the medical centre manufactures them with the corresponding safety guarantees.
- With regards to the **“industrial” production** in the case of unmet need (3D printing or manufacture for other centres) Section 5.5 of the European Regulation (EU) 2017/745 explicitly rules out the “in house” manufacture of medical devices. In that case, the AEMPS should issue an exceptional use authorisation using a fast-track procedure, considering the medical emergency situation, and under a clinical investigation procedure.
- It is more convenient to meet the production demand of these health technologies through a centre or company that has the necessary knowledge, team, equipment, materials and optimum quality system to manufacture medical devices, and has already been authorised by the Direcció General d'Ordenació i Regulació Sanitària (DGORS) of the Catalan Health Department or the AEMPS.
- Several initiatives are already covering this problem in Catalunya and Spain, as well as in other countries, with the manufacture of ventilators/respirators or some of their parts with 3D printing technology and with other types of manufacturing too.
- Several institutions and organizations are collecting these initiatives on innovative health technologies. It would be necessary to converge and complement these sources of information collection in order to make the process more efficient and, therefore, the answer to the urgent needs of the health care system.

Recommendations

- To classify the type of health technology in development according to the Directive of medical devices in order to know the applicable regulation and the regulation process.
- To coordinate the different initiative collection sources (Fundació TIC Salut i Social, Institut Català de la Salut, Col·legi Oficial de Metges de Barcelona, ACCIÓ, AQUAS, etc.)
- To create a global collection box for the citizens in Canal Salut that gathers fundamental information with regards to the types of equipment, their regulation and the production volume. An initiatives' suggestion box has been temporarily created through an online application form (for more information contact ATiQ.aquas@gencat.cat).
- To establish a coordinated action process between the different organizations involved in order to:
 - Coordinate the collection of innovative initiatives on health technologies



- Assess the initiatives
- Advice the initiatives through the necessary regulation process
- Formulate recommendations for clinical indications
- Establish the production needs
- Know the distribution, use and results of the devices/health technologies

A transversal group of work has been created in this sense with the participation of the Departament de Salut, the CatSalut, the Servei d'emergències Mèdiques (SEM), the Institut Català de la Salut (ICS), the Departament d'Empresa i Ocupació, Leitat, the Fundació TIC Salut i Social, Eurecat and AQuAS (For more information Contact ATiQ.aquas@gencat.cat).



Special approval procedure through a clinical investigation process

The public health crisis triggered by COVID-19 caused a large and increasing number of patients to need invasive ventilatory support in the intensive care units. This situation involves the necessity to use more mechanical ventilators than those usually available. This implied several consultations of projects to manufacture respirators / ventilators (using 3D printing technology or new prototypes⁴). These are considered medical devices (class IIb) and therefore are regulated by European Directive concerning medical devices 93/42/CEE of June 14th and Royal Decree 1591/2009 of October 16th that regulates medical devices.

The AEMPS has drawn up a set of guidelines regarding the use of these devices in safety conditions in order to speed up their availability in hospitals (INFORMATION ON THE VENTILATOR PROTOTYPES, SAFETY TESTS AND CLINICAL INVESTIGATION REQUIREMENTS¹). These guidelines also set the technical documentation and minimum tests that have to be carried out on the devices before using them on patients within a clinical investigation that always prioritizes the safety of the patients. The necessary information regarding other devices classed in a similar way (Class II) will probably be similar. Please see summary on Table 1.

The TECHNICAL DOCUMENTATION with complete and detailed information on the prototype (including the results of the preclinical trials), has to be sent to the AEMPS⁵ for assessment before applying for the authorisation of the clinical investigation. In order to help put together all the documentation, the different requirements requested by the AEMPS are provided in a template (for more information contact ATiQ.aguas@gencat.cat).

Once the previous results have been revised, a clinical investigation has to be requested to the AEMPS in order to be able to be used on humans.

The clinical investigation of medical devices is regulated by Royal Decree 1591/2009 that regulates medical devices, and Royal Decree 1616/2009 that regulates active implantable medical devices. The investigation has to be authorised by the AEMPS and obtain the favourable opinion of the Clinical research ethics committee as well as the approval of the responsible managers of the centres that participate in the investigation.



Table 1. Special approval procedure through a clinical investigation process and information requirements (adjustment)*

PRODECURE PHASES	REQUIREMENTS	SPECIFIC ASPECTS
TECHNICAL DOCUMENTATION (This information should be sent to pscontrol@aemps.es)	Technical specifications and design of the developed ventilator prototypes.	Purpose Use settings Description of the main functional parts (parts, components and raw materials), Visual images such as diagrams, photographs and drawings with the corresponding explanations Functional specifications to guarantee a safe use Instructions of use and labelling.
	Identification of already marketed similar devices and determination of the degree of technical, functional and clinical equivalency	
	Brief analysis of the risks	
	Identification of the safety and working requirements, and used methods to check their safety and that they work correctly	**
	Description of the manufacturing process and routine controls to be carried out	
	Results of the preclinical trials carried out	Working tests carried out with human models, patient simulators and/or artificial lungs. Results of the translational validation in the porcine model Functional safety tests of the ventilator prototype
CLINICAL INVESTIGATION Once the technical documentation has been revised, the clinical investigation request will be sent to: psinvclinic@aemps.es	Title of the investigation	
	Centres where the investigation will take place and contact information of the person to send the authorisation to.	
	Name of the developer	Physical person, company, institution or organization responsible of starting, managing and organising the financing of the clinical investigation, e.g. the developer could be the manufacturer or designer of the prototype, a foundation, a hospital, etc.
	Ethical Committee Approval	
	Approval of the Management of the centre	
	Main researcher	Person responsible for a team of researchers that carried out a clinical investigation in a centre
	Conformance of the AEMPS with the tests and technical documentation filed	



PRODECURE PHASES	REQUIREMENTS	SPECIFIC ASPECTS
	Research protocol*** abbreviated and signed by the main researcher that must include at least:	Title of the clinical investigation Justification Objective Patients' inclusion and exclusion criteria Parameters to measure that it is safe and effective, methods and when will they be measured Description of the foreseen treatment of the information A researcher handbook document that explains the ventilators, their specifications, how are they manufactured, which tests have been carried out on them (functional, human models, simulators, artificial lungs, etc) and analysis of risks. Patient follow up plan and incident reporting. Instructions of use and labelling for the ventilators to make clear that they are for clinical investigation only

Source: https://www.aemps.gob.es/informa/notasInformativas/productosSanitarios/2020/NI-PS_11-2020-respiradores-pruebas-investigaciones.pdf?x33378

* Before the AEMPS elaborated this document regarding ventilators, another reference document is the one published by the Medicines and Healthcare products Regulation Agency (MHRA) regarding the Rapidly Manufactured Ventilator System (RMVS). Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/876167/RMVS001_v3.1.pdf

** AEMPS has distributed a document on the BASIC MINIMUM REQUIREMENTS FOR THE AUTOMATIC ACTIONING SYSTEMS FOR RESPIRATORS carried out by the Fundación para el fomento de la innovación industrial considering the safety regulations of the electromedical equipment UNE-EN 60601 (available at AQuAS: ATiQ.aquas@gencat.cat).

*** AEMPS will publish or distribute a model of Protocol for clinical investigation.

Other additional elements to consider in this procedure are as follows:

- The proposal of prototype should be as similar as possible to the conventional device (e.g. a conventional ventilator).
- The preclinical trials carried out with animal models should include clinical conditions as similar as possible to the real ones (lungs with respiratory distress simulation, other less extreme situations).
- The approval process will have to start again in case of any proposal of changes to the components / mechanisms, etc.
- Durability tests to carry out: technical durability (48 hours) and durability on porcine animal model: 2h initial test to go to the Ethical Committee and a second test of 6-12 hours (to be confirmed by the AEMPS).



- The inclusion or exclusion criteria of the clinical investigation protocol should establish which patients will be eligible for the device at study (e.g. patients not eligible for a conventional mechanical ventilator by medical prescription).
- A comparative with other devices is not required, but a proof of concept carried out in some patients is (2-4 patients). The number of tests required has not been fixed.
- There has to be a commitment to record the use of the devices in order to identify and notify any adverse incident that may occur (communication of adverse effects through the usual mechanisms).
- It is not necessary to send the developed ventilator to the AEMPS.
- The devices will not bear the CE marking.
- A new application form will have to be filled in order to manufacture devices (exceptionally approved) in another company / centre.

On the other hand, with regards to the clinical investigation with medical devices the project's unique opinion (dictamen único) applies. Therefore, with the assessment and the approval of one Clinical research ethics committee, the project can be carried out in all the hospital centres in Catalunya. The authorisation of each participant centre is also needed. A contract between the developer and the management of each hospital centre is also required.

With regards to the initiatives taking place in Catalunya, one should bear in mind that the Intensive Care Units (ICU) are currently under the unique command of the Hospital Vall d'Hebron.

Table 2 summarizes the latest updated versions of the initiatives identified in Catalunya on mechanical ventilation and their regulation.



Table 2. Initiatives identified in Catalunya on mechanical ventilation: characteristics and regulation*

Name	Type	Technical documentación	Clinical investigación (AEMPS approval)	Nivel de desarrollo	Puntos críticos
OxyGEN	Volumetric	Yes	Yes (under unique ICU Catalonia)	In clinical investigation (AEMPS)	Needs assessment, indications
Leitat1	Volumetric	Yes	Yes (under unique ICU Catalonia)	In clinical investigation (AEMPS)	Needs assessment, indications
DAR	Volumetric	Yes	Yes (under unique ICU Catalonia)	In clinical investigation (AEMPS)	Needs assessment, indications
Respirador Garrotxa	Volumetric	Partial	No	Simulation and animal model, lack safety tests	Support in clinical research design
Respira	Volumetric	Yes	Yes (under unique ICU Catalonia)	In clinical investigation (AEMPS)	Needs assessment, indications
Q-Vent	Pressure	Yes	Yes (under unique ICU Catalonia)	In clinical investigation (AEMPS)	AEMPS approval
Bellvitge	Pressure	Partial	No	Simulation and animal model, lack safety tests	Safety analysis
MAR	Pressure	Partial	No	Simulation tests	Homologation advice
RESP19	Pressure	Partial	No	Prototype production	Homologation advice, time and stock
DARP, IEM, JubicatFM (1)	Pressure	Partial	No	Simulation tests	Risk assessment
DARP, IEM, JubicatFM (2)	First aid kit with O2 for	Partial	No	Simulation tests	Risk assessment



Name	Type	Technical documentación	Clinical investigación (AEMPS approval)	Nivel de desarrollo	Puntos críticos
	diving accidents				
TaurusVent	Volumetric	No	No	Prototype production	Homologation advice and clinical assessment
CDEI-UPC	Volumetric	Partial	No	Simulation tests	Accelerate the approval process
Respiria	Self-inflating mask and bag	Partial	No	Prototype production	Prototype improvements, external dependency, missing info
Respirem	Volumetric and pressure	Partial	No	Simulation tests	Clinical collaboration, homologation info

* Updated May 6th 2020

AEMPS Agencia Española de Medicamentos y Productos Sanitarios

ICU Intensive Care Unit



European Union Regulation

The registration of medical devices within the European Union (EU) is set up according to one of the three Medical Devices Directives (MDD):

- 90/385/EEC on Active Implantable Medical Devices (AIMDD).
- 93/42/EEC on Medical Devices (MDD).
- 98/79/EC on In Vitro Diagnostic Medical Devices (IVDMDD).

The European Commission provides a guidance to assist in implementing the current directives on medical devices in order to ease the understanding of the legal requirements requested⁶. We summarise the main aspects as follows:

Requirements to apply for the registration of a medical device

- To be a manufacturer or to be represented by an EU authorised representative (EC REP) in the case that the legal manufacturer of the device is located outside the EU.
- Technical and scientific documentation that considers the following essential requirements:
 - Safety of the patient
 - Functionality of the device
 - Safety in using the device
 - Transport and storage of the device
 - Risks and advantages
 - Design and manufacture requirements

Classification of ventilators / respirators

They are products used for anaesthesia and respiration, classified as systems of administration of medicinal gases (Class IIb).

Class IIb: The devices that imply a medium risk to the patients and can be subject to a quality assessment system, as well as the certification of third-party devices and the system's devices. They are in general partially or totally implantable and could modify the biological or chemical composition of body fluids.

As previously explained, before the pandemic situation caused by Covid-19, on March 27th 2020 the AEMPS elaborated the guidelines to carry out a special approval procedure through a clinical investigation process (https://www.aemps.gob.es/informa/notasInformativas/productosSanitarios/2020/NI-PS_11-2020-respiradores-pruebas-investigaciones.pdf?x33378).

The requirements to apply for the approval of these devices (CE marking) in a normal situation would be as shown in the following table.



Table 3. Requirements to process the regulation approval (CE marking) of the medical devices class IIb

Requirements
To establish the type of device
To implement a Quality Management System ^a
Clinical trials (to prove "Safety"; "Effectiveness" (functionality) as a desirable requirement).
Technical dossier or file (documentation to prove compliance of the essential requirements ^b).
Design dossier (only for class III: technical information dossier and data on the randomized clinical trials).
Risk management ^c
To establish the legal manufacturer of the device.
Registration within a "competent authority" (AEMPS delegate as Notified Body).
Conformity Statement
CE marking

a Certification to ISO 13485 and the compliance with a quality system are necessary to obtain the CE marking approval.

b Compliance with 14 "essential requirements" (plus other 54 subsets) listed in Annex I of the Medical Devices Directive (MDD). A more detailed analysis of the clinical safety and the use of the device are requested for devices class IIa and IIb.

c The reference rule and the more applied one in terms of risk management is ISO 14971.

Classification of other devices related to mechanical ventilation

T connectors (splitters) and other devices to multiply the capacity of the ventilator (and other ICU components).

These products are not considered to be medical devices. They can be used under medical criteria with the previous validation of their functionality and the approval of the hospital where they will be used. The quality of these pieces or units must be guaranteed checking their medical validation, quality of the material, the non-detachment of particles when subject to air flow and the absence of organic volatile solvents (depending on the manufacturing technology), microbiological quality and/or sterility.

No previous authorisation from the AEMPS is needed. This will also apply to the spare parts used in the ICUs.

Masks and helmets with adaptors to use in CPAP.

They are medical devices. Given the exceptional situation caused by Covid-19, the hospital that wants to use them has to request an AEMPS' authorisation to use them as compassionate use. The application form to the AEMPS has to include information on their medical validation, an analysis of the risks and quality of the unit manufactured for the adaptation (quality of the



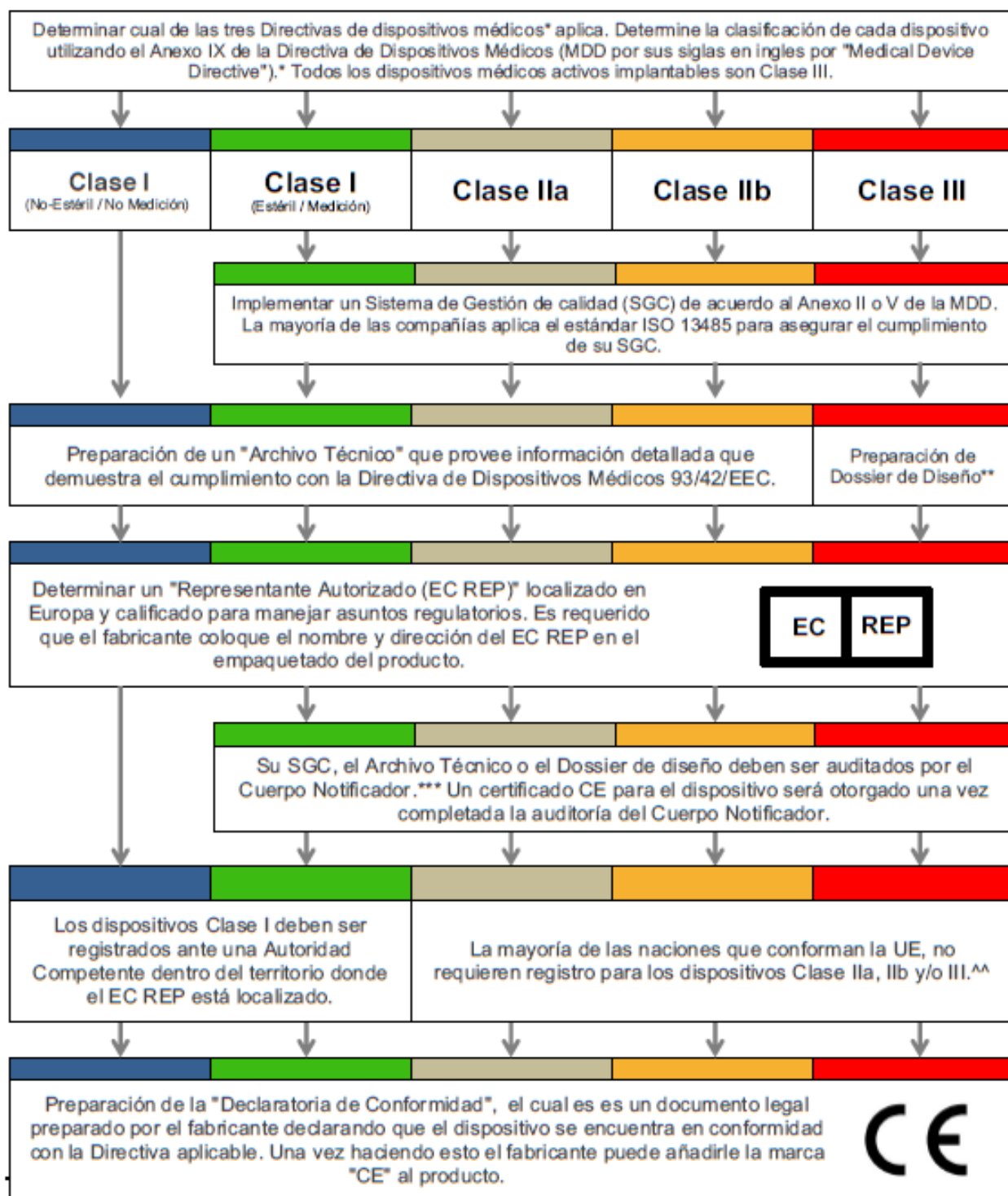
material, the non-detachment of particles when subject to air flow and the absence of organic volatile solvents (depending on the manufacturing technology). When authorised by the AEMPS they can be used for different patients. No individual patient authorisation is required. The patient will have to give its informed consent before using them.

In a normal situation the fast-track approval through compassionate use is not a possibility to be considered as it was abolished in 2004 with regards to medical devices (however it is still available on the AEMPS' web).

The connector used to connect the different components that form the CPAP is not a medical device itself and could have the same consideration as a splitter for ventilators.



EUROPEAN REGULATION CHART



Source: Adapted EMERGO Group

* The European Directives applicable to medical devices are the Directive on Medical Devices (93/42/CEE) and the Directive on Active Implantable Medical Devices (90/385/CEE) modified by Directive 2007/47/CE. The above chart does not apply to In Vitro Diagnostic Medical Devices that are regulated by the Directive on In Vitro Diagnostic Medical Devices (98/79/CE).

** Class III devices as well as implantable devices could request a large amount of clinical information to be approved. The clinical trials carried out in Europe must be previously



approved by a competent authority. The existing clinical data can be acceptable. All the data is revised and approved by the Notified Body.

*** Notified Body = Means a third party accredited within EU to carry out company audits of medical device companies.

^ A CE marking (issued by a Notified Body) is not applicable to Class I devices, non-sterile or non-measurable devices, as the manufacturers can "self-certify" the conformity with the Directive.

^ ^ Competent authority = Term used to describe the national health ministries responsible to guarantee the compliance with the corresponding regulations, laws or directives of their national markets.

^ ^ ^ Currently some countries demand the registration of all devices despite their classification. Other countries only demand the registration of high-risk devices.

“In house” manufacturing

The European Union passed a new regulation (EU 2017/745) on medical devices which enforcement had to be effective from May 26th 2020 (term which will probably be extended due to the current coronavirus situation). This regulation authorises hospital managers to develop their own material in record time. Therefore, the EU authorises hospital managers to create and use their own ventilators if they are designed in the hospital premises. They are not allowed to use them in other hospitals or market them.

This is known as “in house” manufacture (that is, ventilators designed and manufactured in the hospital and used exclusively in said hospital) with 3D printing technology or any other technology, CE marking is not necessary⁷. In this case there is no interest in marketing them, there are no other alternatives in the market and the medical centre manufactures them with the corresponding safety guarantees.

The new Regulation does not specify terms, only the compliance with minimum standards and the liability of the managers of the medical centres.



Acknowledgments

This report is a summary translation into English of the AQUAS report **Ventiladors mecànics i altres dispositius sanitaris per la crisi de la Covid-19: iniciatives, regulació i recomanacions** that has been possible thanks to the disinterested collaboration of Cristina García Ventura.

References

¹ Section 10.3.i) of Royal Decree 1087/2003 of 29 August (B.O.E. 30-0803) that sets the organic organization of the Health and Consumption Ministry, states that "the AEMPS should authorise, suspend or restrict the exceptional use of some medical devices in the interest of health".

² INFORMATION ON THE VENTILATOR PROTOTYPES, SAFETY TESTS AND CLINICAL INVESTIGATION REQUIREMENTS. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) (https://www.aemps.gob.es/informa/notasInformativas/productosSanitarios/2020/NI-PS_11-2020-respiradores-pruebas-investigaciones.pdf?x33378)

³ Regulation EU 2017/745 on medical devices (<https://eur-lex.europa.eu/legal-content/ES/TXT/PDF/?uri=CELEX:32017R0745&from=ES>)

⁴ <https://www.aemps.gob.es/informa/notasInformativas/productosSanitarios/2020-productosSanitarios/situacion-actual-de-evaluacion-de-respiradores-artificiales-en-proceso-de-autorizacion-por-la-aemps/>

⁵ Template provided by Leitat Centre Tecnològic (<https://www.leitat.org/castellano/>)

⁶ https://ec.europa.eu/growth/sectors/medical-devices/current-directives/guidance_en

⁷ Regulation EU 2017/745 on medical devices (<https://eur-lex.europa.eu/legal-content/ES/TXT/PDF/?uri=CELEX:32017R0745&from=ES>)